Remarks

The Office Action mailed July 19, 2002 has been received and reviewed. Claims 1-43, 49, 55, and 61-63 having been canceled, claims 44, 45, 50, 51, and 57 having been amended, the pending claims are claims 44-48, 50-54, and 56-60. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim 44 has been amended for clarification by deleting the word "substantially." Claims 45, 51, and 57 have been amended for clarification by reciting the language "further comprises." Claim 50 has been amended to recite "a wild-type polymorphism oligonucleotide probe," which is supported by the specification at, for example, page 17, line 11 to page 18, line 7.

Proposed Drawing Corrections

The Examiner noted the receipt of Figures including hand-written notations in red. On October 18, 2001, Applicant submitted proposed corrected drawings to replace originally filed sheets 4, 5, 7, 8, 11, 12, 13, 16 and 18, which relate to Figures 4, 5, 7, 8, 11, 12, 13, 17, and 19. The proposed corrections identify the sequences contained therein with the assigned SEQ ID NO. These changes were shown in red on the corrected drawings. Per M.P.E.P. §§608.02(h) and 608.02(v), Applicant respectfully requests that the Examiner enter the corrected drawings. Notification of entry of the corrected drawings in the next Official Communication is again respectfully requested.

To address the issues noted in the Notice of Draftperson's Patent Drawing Review (PTO-948) mailed with an Official Communication on August 22, 2001, Applicant respectfully proposes to submit Formal Drawings after notification of entry of the corrected drawings and receipt of a Notice of Allowability.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 44-48, 50-54 and 56-60 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner alleged that the terms "comprises" and "comprising" render the metes and bounds of claims 44, 50, and 56 indefinite. Applicant respectfully disagrees. The M.P.E.P. clearly indicates that comprising is an accepted transitional phrase (*see, for example* §2111.03, stating that "[t]he transitional term 'comprising', which is synonymous with 'including,' 'containing,' or 'characterized by,' is inclusive or open-ended and does not exclude additional, unrecited elements or method steps"). Applicant respectfully submits that the terms "comprises" and "comprising" are not indefinite, and that claims 44, 50, and 56 particularly point out and distinctly claim the subject matter that Applicant regards as his invention.

The Examiner also alleged that the term "substantially" in claims 44 and 56 is "per se indefinite." Applicant respectfully disagrees. The term substantially has been held to be definite (e.g., M.P.E.P. §2173.05(b)(D), citing a holding that "the limitation 'to substantially increase the efficiency of the compound as a copper extractant' was definite in view of the general guidelines contained in the specification"). The present specification provides the following general guidelines:

> The chemically modified autoligating oligonucleotides bind to a polynucleotide template or target substantially adjacent to each other. Oligonucleotides bind to a template or target polynucleotide "substantially adjacent" to each other when the 5' end of the "upstream" nucleotide binds to a base on the template or target polynucleotide that is directly adjacent to (see Figure 1), or within 2 bases either side of, preferably within about 1 base either side of, a base on the template or target polynucleotide bound by the 3' end of the "downstream" nucleotide. The term "substantially adjacent" thus includes, for example, oligonucleotides that are bound to the template or target polynucleotide directly adjacent to each other; oligonucleotides bound to the template or target polynucleotide such that there is a gap of 1 or 2 bases between the "upstream" and "downstream" oligonucleotide; and oligonucleotides bound to the template or target polynucleotide such that

> there is a 1 or 2 nucleotide overlap between the two oligonucleotides. When bound to a polynucleotide template or target substantially adjacent to each other, the upstream and downstream oligonucleotides self-ligate due to their close proximity and the presence of reactive groups on their adjacent ends. Chemically modified oligonucleotides that bind to a template or target polynucleotide directly adjacent to each other are, of course, preferred, but the method of invention is by no means limited to directly adjacent binding.

Thus, Applicant respectfully submits that the term "substantially adjacent" is definite in view of the general guidelines contained in the specification. Moreover, in the interest of expediting the prosecution of the present application, claim 44 has been amended to delete the word "substantially."

In addition, the Examiner alleged that the term "detecting" in each of claims 44, 50, and 56 renders each of the claims incomplete, because allegedly "the noted claims fail to provide for any substituents on the noted starting compounds, or products which would permit detection." Applicant respectfully disagrees. Applicant respectfully submits that such substituents (e.g., detectable labels), although preferred, are not required to permit detection, as clearly stated in the specification: "Preferably, at least one of the oligonucleotide probes is detectably labeled so that at least one of the ligation products is thereby labeled, although ligation events also can be detected using PCR, rolling circle amplification, gel electrophoresis or the like *without detectably labeling the ligation products*" (page 19, lines 12-15; emphasis added). Thus, Applicant respectfully submits that claims 44, 50, and 56 are complete.

Finally, the Examiner alleged that claims 45, 51, and 57 lack proper antecedent basis, because there is no provision in any of claims 44, 50, and 56 for detectable substituents on any of the starting materials or products. Applicant respectfully submits that claims 45, 51, and 57 clearly and distinctly convey Applicant's invention to one of skill in the art. However, in the interest of expediting the prosecution of the present application, claims 45, 51, and 57 have been amended to recite the language "further comprising," and the rejection is obviated.

Applicant respectfully requests that the rejections under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

Rejection under 35 U.S.C. §102

The Examiner rejected claims 44-48, 50-54 and 56-60 under 35 U.S.C. §102(b) as allegedly being anticipated by PCT International Application Publication No. WO 96/35699 ('699; "AM"). The Examiner also alleged that the following documents each include anticipatory subject matter and are therefore effective equivalents to '699: U.S. Pat. Nos. 5,476,930 (Letsinger et al.; "AA"), 5,571,903 (Gryaznov; "AB"), 5,681,943 (Letsinger et al.; "AC"), and 5,780,613 (Letsinger et al.; "AF"); Gryaznov et al., *Nucleic Acids Research*, 22:2366-2369 (1994) ("AW"); Gryaznov et al., *J. Am. Chem. Soc.*, 115:3808-3809 (1993) ("AU"); PCT International Application Publication No. WO 97/05284 ("AO"); Xu et al., *Nucleic Acids Research*, 27:875-881 (1999) ("DV"); Xu et al., *Nucleic Acids Research*, 26:3159-3164 (1998) ("DU"); and Xu et al., *Tetrahedron Letters*, 38:5595-5598 (1997) ("DT"). Applicant respectfully points out that the present application claims the benefit of U.S. Provisional Application Serial No. 60/116,059, filed January 15, 1999. Thus, Applicant notes that Xu et al., *Nucleic Acids Research*, 27:875-881 (1999) ("DV"), with a citation date of February 1, 1999, may be intervening art and as a result may not be available as prior art against the invention as set forth in the priority document. In addition, Xu et al., *Nucleic Acids Research*, 26:3159-3164 (1998) ("DU"), with a citation date of July 1, 1998, is not available as art under 35 U.S.C. 102(b) against the invention as set forth in the priority document. Applicant respectfully traverses the rejection.

"[F]or anticipation under 35 U.S.C. 102, the reference must teach *every aspect* of the claimed invention either explicitly or impliedly." M.P.E.P. §706.02 (emphasis added). Applicant respectfully submits that none of the cited art teaches every aspect of the claimed invention.

First, none of the cited art specifically teaches a method for detecting a genetic polymorphism in a target polynucleotide that includes: providing a mutant polymorphism oligonucleotide probe and a universal oligonucleotide probe, such that, when both probes are bound to the target polynucleotide, an end of the universal oligonucleotide probe *is not directly*

adjacent to an end of the mutant polymorphism oligonucleotide probe; and contacting the target polynucleotide with the universal oligonucleotide probe and the mutant polymorphism oligonucleotide probe to yield an autoligated oligonucleotide product comprising the universal oligonucleotide probe and the mutant polymorphism probe (e.g., claim 44). Applicant respectfully submits that claim 44 and dependent claims 45-48 are not anticipated by the cited art.

Furthermore, none of the cited art specifically teaches a method for detecting a genetic polymorphism in a target polynucleotide that includes: providing a *mutant* polymorphism oligonucleotide probe *of less than 7 nucleotides in length*, a *wild-type* polymorphism oligonucleotide probe *and* a *universal* oligonucleotide probe, such that, when a universal probe and a polymorphism probe are bound to the target polynucleotide, an end of the universal oligonucleotide probe is substantially adjacent to an end of the polymorphism oligonucleotide probe; and contacting the target polynucleotide with the universal oligonucleotide probe, the wild-type oligonucleotide probe and the mutant polymorphism oligonucleotide probe to yield an autoligated oligonucleotide product comprising the universal oligonucleotide probe and either the mutant polymorphism oligonucleotide probe or the wild-type polymorphism oligonucleotide probe (e.g., claim 50). Applicant respectfully submits that claim 50 and dependent claims 51-54 are not anticipated by the cited art.

Finally, none of the cited art specifically teaches a method for detecting a genetic polymorphism in a *target RNA* that includes: providing a mutant polymorphism oligonucleotide probe and a universal oligonucleotide probe, such that, when both probes are bound to the target RNA, an end of the universal oligonucleotide probe is substantially adjacent to an end of the mutant polymorphism oligonucleotide probe; and contacting the target RNA with the universal oligonucleotide probe and the mutant polymorphism oligonucleotide probe to yield an autoligated oligonucleotide product comprising the universal oligonucleotide probe and the mutant polymorphism probe (e.g., claim 56). Applicant respectfully submits that claim 56 and dependent claims 57-60 are not anticipated by the cited art.

Applicant respectfully requests that the rejection under 35 U.S.C. §102 be reconsidered and withdrawn.

Inventorship

The Examiner stated on page 5, line 10 of the Office Action mailed July 19, 2002, that the present application currently names joint inventors. Applicant wishes to correct the record to show that the present application currently names Eric T. Kool as the sole inventor.

Summary

It is respectfully submitted that all the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicant's Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that this paper is being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Assistant Commissioner for Patents, Washington, D.C. 20231, on this 23 day of October, 2002, at 2:07pm (Central Time).

By: _____
Name: SARA E. OLSON

APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS INCLUDING NOTATIONS TO INDICATE CHANGES MADE
Serial No.: 09/483,337
Docket No.: 220.00040101

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted. Additionally, all amendments have been indicated by the use of bold font.

In the Claims

For convenience, all pending claims are shown below.

44. **(Amended)** A method for detecting a genetic polymorphism in a target polynucleotide comprising:

providing a mutant polymorphism oligonucleotide probe that is complementary to a region on the target polynucleotide that comprises the genetic polymorphism;

providing a universal oligonucleotide probe capable of binding to the target polynucleotide at a region that is conserved in the analogous wild-type polynucleotide;

wherein one oligonucleotide probe constitutes an upstream oligonucleotide comprising, as its 5' end, a nucleoside comprising a 5' leaving group and the other oligonucleotide probe constitutes a downstream oligonucleotide comprising, as its 3' end, a nucleoside comprising a 3' functional group selected from the group consisting of a 3' phosphorothioate, a 3' phosphoroselenoate and a 3' phosphorotelluroate, such that, when both probes are bound to the target polynucleotide, an end of the universal oligonucleotide probe is **[substantially but]** not directly adjacent to an end of the mutant polymorphism oligonucleotide probe so as to position the 5' leaving group and the 3' functional group in close proximity to one another;

contacting the target polynucleotide with the universal oligonucleotide probe and the mutant polymorphism oligonucleotide probe to yield an autoligated oligonucleotide product comprising the universal oligonucleotide probe and the mutant polymorphism probe; and

detecting the presence of the autoligated oligonucleotide product.

45. **(Amended)** The method of claim 44 wherein at least one of the mutant polymorphism oligonucleotide probe and the universal oligonucleotide probe **further** comprises a detectable label.

46. The method of claim 45 wherein the detectable label is a radiolabel.

47. The method of claim 44 wherein the genetic polymorphism is selected from the group consisting of a single base mutation, a plurality of single base mutations, a deletion, an insertion, and a genetic rearrangement.

48. The method of claim 44 wherein the nucleotide position of the genetic polymorphism is not the nucleotide position corresponding to the ligation junction end of the mutant polymorphism probe.

50. **(Amended)** A method for detecting a genetic polymorphism in a target polynucleotide comprising:

providing a mutant polymorphism oligonucleotide probe of less than 7 nucleotides in length that is complementary to a region on the target polynucleotide that comprises the genetic polymorphism;

providing a wild-type polymorphism oligonucleotide probe that is complementary to a region on an analogous wild-type polynucleotide that is analogous to the region comprising the genetic polymorphism;

providing a universal oligonucleotide probe capable of binding to the target polynucleotide at a region that is conserved in the analogous wild-type polynucleotide;

wherein **either (i) the universal oligonucleotide probe constitutes an upstream oligonucleotide comprising, as its 5' end, a nucleoside comprising a 5' leaving group and both polymorphism oligonucleotide probes constitute downstream oligonucleotides**

comprising, as their 3' ends, a nucleoside comprising a 3' functional group selected from the group consisting of a 3' phosphorothioate, a 3' phosphoroselenoate and a 3' phosphorotelluroate; or (ii) both polymorphism [one] oligonucleotide **probes constitute** [probe constitutes an] upstream **oligonucleotides** [oligonucleotide] comprising, as **their** [its] 5' **ends** [end], a nucleoside comprising a 5' leaving group and the **universal** [other] oligonucleotide probe constitutes a downstream oligonucleotide comprising, as its 3' end, a nucleoside comprising a 3' functional group selected from the group consisting of a 3' phosphorothioate, a 3' phosphoroselenoate and a 3' phosphorotelluroate, such that, when **a universal probe and a polymorphism probe** [both probes] are bound to the target polynucleotide, an end of the universal oligonucleotide probe is substantially adjacent to an end of the [mutant] polymorphism oligonucleotide probe so as to position the 5' leaving group and the 3' functional **group** in close proximity to one another;

contacting the target polynucleotide with the universal oligonucleotide probe, **the wild-type polymorphism oligonucleotide probe** and the mutant polymorphism oligonucleotide probe to yield an autoligated oligonucleotide product comprising the universal oligonucleotide probe and **either** the mutant polymorphism **oligonucleotide** probe **or the wild-type polymorphism oligonucleotide probe**; and

detecting the presence of the autoligated oligonucleotide product.

51. **(Amended)** The method of claim 50 wherein at least one of the mutant polymorphism oligonucleotide probe and the universal oligonucleotide probe **further** comprises a detectable label.

52. The method of claim 51 wherein the detectable label is a radiolabel.

53. The method of claim 50 wherein the genetic polymorphism is selected from the group consisting of a single base mutation, a plurality of single base mutations, a deletion, an insertion, and a genetic rearrangement.

54. The method of claim 50 wherein the nucleotide position of the genetic polymorphism is not the nucleotide position corresponding to the ligation junction end of the mutant polymorphism probe.

56. A method for detecting a genetic polymorphism in a target RNA comprising:

providing a mutant polymorphism oligonucleotide probe that is complementary to a region on the target RNA that comprises the genetic polymorphism;

providing a universal oligonucleotide probe capable of binding to the target RNA at a region that is conserved in the analogous wild-type RNA;

wherein one oligonucleotide probe constitutes an upstream oligonucleotide comprising, as its 5' end, a nucleoside comprising a 5' leaving group and the other oligonucleotide probe constitutes a downstream oligonucleotide comprising, as its 3' end, a nucleoside comprising a 3' functional group selected from the group consisting of a 3' phosphorothioate, a 3' phosphoroselenoate and a 3' phosphorotelluroate, such that, when both probes are bound to the target RNA, an end of the universal oligonucleotide probe is substantially adjacent to an end of the mutant polymorphism oligonucleotide probe so as to position the 5' leaving group and the 3' functional group in close proximity to one another;

contacting the target RNA with the universal oligonucleotide probe and the mutant polymorphism oligonucleotide probe to yield an autoligated oligonucleotide product comprising the universal oligonucleotide probe and the mutant polymorphism probe; and

detecting the presence of the autoligated oligonucleotide product.

57. **(Amended)** The method of claims 56 wherein at least one of the mutant polymorphism oligonucleotide probe and the universal oligonucleotide probe **further** comprises a detectable label.

58. The method of claim 57 wherein the detectable label is a radiolabel.

59. The method of claim 56 wherein the genetic polymorphism is selected from the group consisting of a single base mutation, a plurality of single base mutations, a deletion, an insertion, and a genetic rearrangement.

60. The method of claim 56 wherein the nucleotide position is not the nucleotide position corresponding to the ligation junction end of the mutant polymorphism probe.